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Cisplatin-Based Chemotherapy After Retroperitoneal Lymph Node Dissection in Patients With Pathological Stage II Nonseminomatous Germ Cell Tumors

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In order to assess the results of cisplatin-based chemotherapy after primary lymph node dissection in patients with pathological stage II nonseminomatous germ cell tumors of the testis, we retrospectively reviewed the long-term outcome of 44 patients who received adjuvant chemotherapy at Institut Gustave Roussy over a 7-year period. Two chemotherapy regimens were sequentially delivered. Twenty-three patients were treated with vinblastine, cyclophosphamide, bleomycin, actinomycin D, and cisplatin (mVAB-6, four cycles), while 21 patients received a combination of etoposide and cisplatin (EP, four cycles). After a median follow-up of 6 years, all patients remain free from progression. The long-term toxicity included retrograde ejaculation in eight patients and severe ototoxicity in two patients. We conclude that four cycles of cisplatin-based chemotherapy for pathological stage II testicular cancer resulted in a 100% cure rate with minimal toxicity.

KEY WORDS: testicular cancer, stage II, adjuvant chemotherapy

INTRODUCTION

The introduction of cisplatin-based combination chemotherapy has greatly improved the survival of patients with metastatic nonseminomatous germ-cell tumors of the testis [1]. Stage II disease is defined as a metastatic disease limited to the retroperitoneal lymph nodes [2]. Prior the advent of cisplatin-based chemotherapy, patients with completely resected stage II disease were offered either no adjuvant therapy, minimally effective non–cisplatin-based chemotherapy, or postoperative radiotherapy. For these patients, the relapse rate ranged from 20% to 70%, with most series showing rates of 50–60% [3–8]. Adjuvant cisplatin-based chemotherapy after retroperitoneal lymph node dissection (RPLND) has been investigated in this setting with the aim of lessening the relapse rate and therefore increasing the long-term cure rate. We report here on our 8-year experience with adjuvant cisplatin-based chemotherapy in patients with pathological stage II nonseminomatous germ-cell tumors of the testis.

PATIENTS AND METHODS

From June 1985 to December 1992, 44 patients with pathological stage II nonseminomatous germ-cell tumors of the testis received adjuvant cisplatin-based chemotherapy at the Institut Gustave Roussy. Prior to RPLND, all patients had undergone a complete clinical examination, abdominal computed tomography (CT) scan, chest X-ray, and radioimmune assays for serum tumor markers (human chorionic gonadotrophin and alphafetoprotein). Thirty-three and 25 patients had additionally undergone a lymphangiogram and a thoracic CT scan, respectively. Nine patients underwent a complete bilateral RPLND, while 35 patients were offered the option of a modified unilateral

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dissection. In 13 patients, the RPLND was performed in our institution, while 31 patients were referred to us from 21 different surgeons. Pathologic staging of retroperitoneal metastases was made according to the following criteria: stage B1 included less than six positive nodes, all located in the primary landing site, with no node greater than 2 cm in diameter and no extracapsular lymph node extension; stage B2 was applied to all other situations.

From June 1985 to October 1988, 23 patients received a modified VAB-6 (mVAB-6) chemotherapy regimen, which consisted of vinblastine 4 mg/m^2/day IV on day 1, actinomycin D 1 mg/m^2/day IV on day 1, cyclophosphamide 600 mg/m^2/day IV on day 1, cisplatin 120 mg/m^2/day on day 1 and bleomycin 20 mg/day IV continuous infusion on days 1–3. Four cycles were delivered every 4 weeks. From November 1988 to December 1992, 21 patients received the EP regimen with etoposide 100 mg/m^2/day on days 1–5 and cisplatin 20 mg/m^2/day on days 1–5. Four cycles were delivered every 3 weeks. Adjuvant chemotherapy was started 3–4 weeks following RPLND. Prior to chemotherapy, patients had a physical examination, chest X-ray, and serum tumor markers. Patients whose serum tumor markers did not return to normal levels were not considered for adjuvant chemotherapy.

After the end of chemotherapy, patients were followed every 3 months in the first 2 years and at increasing intervals thereafter. Progression-free survival as measured from the end of adjuvant chemotherapy until January 1, 1995. All patients were carefully assessed for clinical and biological long-term toxicities.

RESULTS

Forty-four evaluable patients with pathological stage II nonseminomatous germ-cell tumors of the testis received adjuvant cisplatin-based chemotherapy following RPLND. The median age was 23 years (range, 17–53). The tumor developed in the right testicle in 24 cases. No bilateral tumor was observed. All but one patient had an embryonal carcinoma component in the primary tumor (Table I). Before RLND, 26 patients had a disease limited to the testis (stage I), while 18 patients had a radiologic involvement of retroperitoneal lymph nodes (<2cm: 15; 2–5 cm:2; >5 cm: 1). The retroperitoneal dissection identified 17 patients with stage B1 and 27 patients with stage B2, including 10 patients with extranodal tumor extension. The histological pattern is depicted in Table I. All but three patients had an embryonal carcinoma component in the retroperitoneal lymph nodes. The other three patients had an immature teratoma, yolk-sac, and seminoma as the unique pathological component, respectively.

The patients' outcome according to the adjuvant chemotherapy regimen and pathological staging is shown in Table II. No patient experienced recurrent disease. All of them are alive without evidence of disease 24–114 months after the end of chemotherapy. The long-term toxicity included eight patients with retrograde ejaculation, six of whom had undergone a complete bilateral RPLND. However, in two patients who had undergone a modified unilateral dissection, ejaculation could be restored by sympathomimetic drugs, and one of them succeeded in fathering a child. Five other patients fathered six healthy children. Neither clinical pulmonary nor peripheral neurologic toxicity was observed. Two patients developed severe long-term clinical ototoxicity after mVAB-6 therapy.

DISCUSSION

Before the cisplatin era, the results of adjuvant chemotherapy in stage II nonseminomatous germ-cell tumors of the testis demonstrated a 15–70% relapse rate [3–6]. With the successful introduction of cisplatin in the first-line treatment of disseminated disease, subsequent studies in the adjuvant setting resulted in a disease-free survival rate of 85–100%. At the Memorial Sloan Kettering Cancer Center (MSKCC), two regimens, VAB-3 and VAB-6 showed that adjuvant cisplatin-based chemotherapy was nearly able to cure all patients [9,10]. Other institutions reported their experience with a combination of cisplatin, vinblastine, and bleomycin (PVB). Similar excellent results were obtained [5,7,11–13]. Using a modified VAB-6 and an etoposide containing regimen (EP), we confirm in the present study the excellent efficacy of adjuvant cisplatin-based chemotherapy in these stage II patients after primary pathological lymph node dissection. With a median follow-up of 6 years, all 44 patients remain free from progression.

The need for all patients with pathological stage II disease to receive adjuvant chemotherapy is questionable. At the MSKCC, the patients treated with non–cisplatin-based chemotherapy were retrospectively assigned into B1 or B2 disease, No patient with stage B1 had a relapse [4]. Other reports identified patients with completely resected disease at low risk for postoperative relapse [14,15]. It was suggested that observation only could be the treatment of choice in patients with minimal node disease (fewer than six nodes involved, no node larger than 2 cm, no extranodal extension) after retroperitoneal lymphadenectomy. A multicentric randomized trial was conducted by the Testicular Cancer Intergroup to determine whether close observation, with chemotherapy reserved for those patients who experienced a subsequent relapse, resulted in a survival rate equivalent to that observed with systematic adjuvant chemotherapy [7]. Forty-eight (49%) of the 98 patients in the observation arm developed a relapse and required chemotherapy for metastatic disease. No identifiable factors were strongly associated with the risk of relapse. It is noteworthy that 51% of patients in this group had stage B1 disease, suggesting an inordinately favorable prognosis in that arm. Only 1

TABLE I. Histological Patterns in Primary Tumors of the Testis and Retroperitoneal Lymph Nodes

Primary tumor histology	Number of patients	Lymph node dissection histology		
		Pure EC	Mixed including EC without teratoma component	Mixed including teratoma component
With embryonal carcinoma (EC)				
Pure EC	11	10	0	1
Mixed without teratoma component	12	7	5	0
Mixed with teratoma component	20	10	5	5
Without embryonal carcinoma				
Mixed	1	0	1	0
Total	44	27	11	6

TABLE II. Long-Term Outcome of the Patients With Stage II Nonseminomatous Germ Cell Tumors of the Testis According to Pathological Staging and Adjuvant Chemotherapy Regimens

Pathological staging	Chemotherapy regimen		No evidence of disease
	mVAB-6	EP	
B1	11	6	17
B2	12	15	27

mVAB-6: vinblastine + actinomycin-D + cyclophosphamide + cisplatin + bleomycin; EP: etoposide + cisplatin.

of 97 patients assigned to adjuvant therapy had a relapse. After a median follow-up of more than 4 years, no difference was observed in the 96% overall survival in the two groups [7]. In the University of Indiana experience, 18 (37%) of 49 patients who did not receive adjuvant chemotherapy had a subsequent relapse. According to the pathological stage, the relapse rate was superior in patients with stage B2 (55%) as compared with that observed in patients with stage B1 (26%). Only one patient died of progressive disease [8]. Given the large range of surgeons who were involved in the management of our patients, we clearly decided to deliver adjuvant chemotherapy in patients with stage B1 and B2 disease.

The optimal number of chemotherapy cycles that should be administered in the adjuvant setting is related to the quality of the primary surgical resection. One randomized study attempted to evaluate the effect of two vs. four courses of PVB following a complete bilateral RPLND [12]. After a median follow-up of 43 months, relapses occurred in 6 of 114 patients who had received two courses and in 1 of 111 patients who had received four cycles. These results were not statistically different. Moreover, patient compliance differed. In the two-course regimen, 108 patients (96%) finished treatment as scheduled, whereas 77 (71%) patients receiving the four-course regimen completed therapy, largely because of toxicity. It is noteworthy that in this study, unlike other PVB regimens, bleomycin was administered at higher doses. The authors concluded that two courses of PVB was sufficient in the adjuvant setting after bilateral RPLND. Whether two cycles of PVB using standard doses of bleomycin are optimal following a modified unilateral dissection in a multicentric practice is a question that is not solved. All patients in our study received four cycles of chemotherapy because of the heterogeneity in the surgical management of our patients.

It is noteworthy that no report dealing with the role of etoposide-based regimens in the adjuvant setting had been published before 1995. If we refer to the treatment of disseminated disease, a randomized trial comparing PVB and BEP (bleomycin + etoposide + cisplatin) showed that etoposide was at least as effective and was less toxic in this setting [16]. In patients with low volume metastatic disease, three cycles of BEP represent the optimal option [17]. However, the efficacy is lower when bleomycin is deleted and four cycles are then required [18]. In our series, bleomycin was deleted with the aim of decreasing toxicity. Investigators at the Memorial Sloan Kettering Cancer Center recently reported their experience with two cycles of the EP regimen as adjuvant treatment after RPLND [19]. All 50 patients who were included in the study achieved a relapse-free status after a median follow-up of 3 years. These results suggest that two cycles of EP could be an optimal adjuvant chemotherapy regimen.

Additionally, the deletion of bleomycin could decrease the toxicity without impairing the efficacy of adjuvant chemotherapy. However etoposide has recently been associated with the development of acute leukemias. This treatment complication may be dose and schedule dependent [20]. In the initial study reported by Pedersen-Bjergaard, five acute leukemias or myelodysplastic syndromes occurred among 212 patients after etoposide therapy. All five patients had received more than 2,000 mg/m^2 of etoposide, that is, at least four cycles of chemotherapy [21]. Of 348 metastatic germ cell tumor patients treated with three to four cycles of BEP as first-line therapy at Indiana University, two developed treatment-related leukemia. None of 67 patients who received only three courses developed this complication [22]. With the aim of limiting the treatment-related side effects, it is clear that adjuvant etoposide-based chemotherapy should no include more than three cycles.

In our population, the long-term toxicity of chemotherapy was minimal. Only the severe ototoxicity observed in two patients could have been alleviated with lower cumulative doses if cisplatin. We conclude that with appropriate precautions, four courses of adjuvant therapy seem worth the 100% cure rate attained in this series of patients.

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